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Three-Dimensional "BURST" Functional Magnetic Resonance Imaging: Initial Clinical Applications

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Measurement of regional hemodynamics in vivo has the potential for widespread clinical use because of the established relationship between neuronal function, energy metabolism, and localized blood supply [1–4]. Functional neuroimaging tools such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), xenon CT scanning, and functional magnetic resonance (fMR) imaging can be used to measure cerebral perfusion in vivo and might prove useful in a variety of clinical situations: (1) to identify the extent of high-risk areas and monitor the effect of therapy in cerebrovascular disorders such as carotid stenosis, cerebral infarcts, and cerebral vascular malformations; (2) to diagnose and screen degenerative disorders such as Alzheimer's disease and evaluate the effect of experimental therapies in these conditions; (3) to stage brain tumors and identify recurrence of tumor versus necrosis after treatment; and (4) to identify epileptogenic foci.

PET, SPECT, and CT, although they can be used to measure regional hemodynamics, are limited in spatial and temporal resolution and involve exposure to radiation, which limits the number of studies that can be done. PET is restricted further to use by research centers and university hospitals because it requires a cyclotron. The rapid advances in the development of fast imaging methods for MR imaging in recent years have made it possible to study brain perfusion using MR imaging. A variety of T2* fMR imaging methods such as echoplanar imaging (EPI) [5], fast low-angle shot (FLASH) [6], and related techniques such as echoplanar imaging with signal targeting and alternating radiofrequency [7] and echo-shifted-FLASH [8–10] have become available. FLASH techniques, because of limits on temporal resolution, are restricted to imaging only a few slices. Therefore, to study the whole brain, techniques with superior temporal resolution are required. EPI, a technique with superior temporal resolution, can image multiple slices within a few seconds; it is, however, limited by the need for dedicated hardware.

Recently, Duyn et al. [11, 12] introduced frequency-shifted (FS-BURST), a fast T2*-sensitized imaging technique capable of three-dimensional imaging of the whole brain in 2.2 sec. It has equal T2* weighting over k-space lines

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and can be performed on conventional scanners. Using intravenous administration of a bolus of gadopentetate dimeglumine and the principle of susceptibility-induced signal losses on passage of the contrast agent through the microvasculature, Duyn et al. showed the value of this technique in estimating relative cerebral blood volume (CBV). In this study, we report our results on the initial use of this technique to study neurologic disorders such as Alzheimer's disease and cerebrovascular disease.

MATERIALS AND METHODS

This study was approved by the Intramural Review Board of the National Institute of Mental Health at the National Institutes of Health and the Joint Committee for Clinical Investigation of the Johns Hopkins School of Medicine. We studied four young healthy volunteers (mean age = 25 years), six older healthy volunteers age matched to the patients with senile dementia of the Alzheimer's type (SDAT; mean age = 71 years), six patients with SDAT (mean age = 70 years), two patients with high-grade carotid artery stenosis (one 56-year-old man with stenosis of the right carotid artery and one 60-year-old woman with stenosis of the left carotid artery), and one 39-year-old woman with a subacute cerebral infarction in the distribution of the left middle cerebral artery (MCA).

Imaging was done on a Signa 1.5-T scanner (General Electric Medical Systems, Milwaukee, WI) using a standard quadrature head coil and shielded gradients. The FSBURST pulse sequence [12] has an effective echo time (TE) of 28.8 msec and a repetition time (TR) of 45 msec. Sixty three-dimensional whole-brain volumes, each with 48 oblique (coronoaxial) slices, were acquired in approximately 2 min 12 sec. After 10 baseline volumes were acquired, 0.13 mmol/kg of gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) was administered intravenously as a bolus in all subjects except the patient with subacute infarction of the left MCA. The bolus was administered at 6 ml/sec via a mechanical injector (Medrad, Pittsburgh, PA) through an 18-gauge catheter placed in an antecubital vein. The total injection time was usually 3–5 sec. In the patient with subacute infarction of the left MCA, a 0.15 mmol/kg dose was injected manually within 6–10 sec. Vital signs were monitored, and a questionnaire was given to all subjects to record side effects from the bolus administration of contrast material.

All six patients with SDAT also underwent SPECT–hexamethylpropyleneamine oxime (HMPAO) scans of cerebral blood flow. The scans were acquired on a dedicated head scanner (Ceraspect; DSI, Waltham, MA) equipped with a high-resolution collimator, yielding an image resolution of approximately 7.5 mm full width at half-maximum intensity. Each patient received approximately 10 mCi of ^{99m}Tc-HMPAO intravenously 10 min before data acquisition. Scans were acquired during a 20-min period.

MR imaging data were analyzed off-line using UNIX-based workstations with IDL processing software (Research Systems, Boulder, CO). A two-dimensional fast Fourier transform was used to generate a 40 × 48 × 36 image volume (4 × 4 × 6.11 mm voxels) of each time point. For each voxel in each three-dimensional volume, signal intensity was converted to concentration (C) using the following relationship:

$$C(t) = -k\, ln[S(t)/S_O]$$

in which $S(t)$ is the signal intensity at each time t, S_o is the baseline signal intensity, and k is the proportionality constant correcting for TE, field strength, and contrast agent used [5, 13, 14]. Maps of relative CBV were created in patients with cerebrovascular disease from concentration versus time plots as described by Duyn et al. [12]. In patients with SDAT and age-matched control subjects, low signal-to-noise ratio (SNR) in the images resulted in poor curve fitting and dropping out of many pixels. The reasons for poor SNR in this group are uncertain, but they probably include movement and tissue atrophy. To circumvent the SNR problem, relative CBV maps were created in these patients using the maximum peak concentration value of the curve for each voxel. We chose this method as it can be a sensitive measure of blood volume with bolus tracking [6] and is advantageous for methods with low SNR. These relative CBV maps were then normalized by dividing the relative CBV in each voxel by the global mean relative CBV. In addition, in patients with cerebrovascular disease, "time-to-peak" maps were created from the time taken for the bolus to reach peak concentration in each voxel. The three-dimensional data were then resliced in the axial plane using the ANALYZE software program (version 7.1; Biomedical Imaging Resource, Mayo Foundation, Rochester, MN).

Further analysis was performed as follows:

In patients with cerebrovascular disorders, the relative CBV maps and time-to-peak maps were visually interpreted.

In patients with SDAT and age-matched control subjects, further analysis was done in two ways: (1) Visual

interpretation was done by a physician who was unaware of the clinical diagnosis and was experienced in interpreting functional imaging studies such as PET and SPECT in patients with SDAT, looking for patterns of cortical abnormalities that are characteristic of SDAT. The results from this interpretation then were compared with the SPECT relative CBF data of patients with SDAT. (2) In a region-of-interest analysis, signal-intensity values on the relative CBV maps ranged from 0 to 255. Pixels overlying major vascular structures usually had signal-intensity values greater than 110. These pixels were excluded from further analysis by selecting a cutoff value that ranged from 110 to 150 depending on the individual characteristics of each scan. After this procedure, the maps were examined visually to ascertain that the selection of an individual cutoff value for each subject did not exclude brain tissue or include vascular structures. Subsequently, regions of interest were drawn in the first FS-BURST volume (because this had better anatomic delineation than did the relative CBV maps) in the temporal, frontal, parietal, occipital, and cerebellar areas in many slices in which these regions could be identified clearly by referring to standard atlases. The regions of interest were then applied by computer to the relative CBV maps.

Mean relative CBV values and standard deviations for each region of interest were calculated for each slice. Because the analysis of regions of interest in this study was an exploratory attempt to confirm what was seen on visual interpretation of the scans, the regions of interest with the most extreme values in each subject were selected. A two-tailed Student's *t* test was done between the lowest mean relative CBV values of the patients with SDAT and the age-matched control subjects for each region. The regions of interest with the lowest regional CBV in each patient with SDAT and each control subject also were compared with the corresponding mean regional relative CBV of the control subjects; any region of interest with a relative CBV value more than 1 *SD* below the mean value from a corresponding region of interest in the age-matched control subjects was judged as having decreased perfusion.

RESULTS

In the patient with the subacute cerebral infarction, the relative CBV map revealed visually appreciable decrease in CBV in the infarct region. The time-to-peak map showed a larger area of perfusion deficit than that seen on the relative CBV map; this might represent the tissue at risk and its extent. There was a time-to-peak delay of 5–7 sec within and around the infarct.

In the two patients with high-grade carotid stenosis, no areas of decreased perfusion could be seen on the relative CBV maps. The time-to-peak map, on the other hand, revealed delayed perfusion in the left MCA distribution in the patient with stenosis of the left internal carotid artery with collateral supply from the right internal carotid artery via the anterior communicating artery (as seen on the angiogram). No deficit could be identified in the patient with stenosis of the right internal carotid artery with collateral supply from the ipsilateral external carotid artery.

Among the patients with SDAT, visual interpretation showed that the fMR image detail was qualitatively superior to the detail on the SPECT scans, in part because of motion artifact in the latter. In four of the patients with SDAT, focal defects in the parietotemporal cortex were seen that corresponded to the patterns seen on SPECT scans. The fMR imaging relative CBV maps of two of the six age-matched control subjects were also interpreted as showing perfusion deficits in the parietotemporal distribution.

Region-of-interest analysis showed that CBV was significantly lower in patients with SDAT in the parietal ($p < .029$) and temporal regions ($p < .014$) than in the healthy volunteers (Tables 1 and 2). Five of the six patients with SDAT and one of the six volunteers were categorized as having decreased perfusion in the parietotemporal cortex (i.e., relative CBV data outside of normal mean).

CONCLUSIONS

With the development of ultrafast methods, MR imaging now offers the unique potential to acquire both functional and anatomic data during the same scanning session. FS-BURST is an ultrafast three-dimensional

TABLE 1: Mean Relative Cerebral Blood Volume in Regions of Interest with Lowest Cerebral Blood Volume as Measured by Three-Dimensional Frequency-Shifted BURST Functional Magnetic Resonance Imaging

Region	Controls	Alzheimer's	p^a
Parietal	40.61 ± 11.00	27.91 ± 5.25	.029
Temporal	40.72 ± 6.67	29.93 ± 7.22	.014
Frontal	41.34 ± 6.80	33.80 ± 5.46	.078
Occipital	42.52 ± 11.51	38.20 ± 10.83	.434
Cerebellum	48.57 ± 12.92	42.54 ± 5.71	.224

[a]Two-tailed. Values are mean ± standard deviation.

TABLE 2: Sensitivity and Specificity of Frequency-Shifted BURST Functional Magnetic Resonance Imaging Versus Single-Photon Emission Computed Tomography (SPECT) Relative Cerebral Blood Flow Data in Patients with Senile Dementia of the Alzheimer's Type

Variable	FS-BURST fMR Imaging		SPECT	
	Visual Interpretation	Region-of-Interest Analysis[a]	Claus et al. [18]	Bonte et al. [17]
Sensitivity (%)	66	83	56–79	85–87
Specificity (%)	66	83	90	64–74

FS-BURST fMR imaging = frequency-shifted BURST functional magnetic resonance imaging, SPECT = single-photon emission computed tomography.
[a]Region-of-interest value < 1*SD* of normal mean.

functional imaging technique available on conventionally configured MR scanners and can be used to measure regional cerebral hemodynamics over the whole brain. It can be added to routine MR imaging of patients, requiring additional imaging time of 3–5 min only and with no added discomfort to the patients.

Using time-to-peak maps, we observed what appeared to be the penumbra region in the patient with a subacute infarction in the distribution of the left MCA and a region with slow flow in one patient with severe carotid stenosis. Such information obtained sequentially can be useful for assessing the potential benefit of ongoing stroke therapy and possibly in evaluating new stroke therapies.

Nuclear scanning techniques (e.g., PET, SPECT) have identified a characteristic although nondiagnostic pattern of cortical perfusion (decreased perfusion, especially in the parietal and temporal regions) in most patients with SDAT [15, 16]. In the present study, using region-of-interest analysis, five out of six subjects in each group (patients with SDAT and age-matched control subjects) were identified correctly. Although the number of subjects studied was small, the sensitivity and specificity of this technique (83%) are at least comparable to those obtained by groups using SPECT perfusion techniques [17, 18]. Our region-of-interest analysis, however, deserves a note of caution. We selected the regions of interest with the extreme lowest values to maximize the pathologic hit rate. Although the finding that patients with SDAT are more often deviant on this analysis could indicate that they have more disease, it also might reflect heightened proneness of the group to scanning artifacts such as motion. Although we cannot exclude this, it seems unlikely that artifacts would affect only the data in regions of classic Alzheimer's disease (e.g., temporal and parietal cortices).

Results from these initial studies in patients with dementia and cerebrovascular disorders are encouraging and illustrate the technique's potential to identify dysfunctional areas in neurologic disorders. This method is noninvasive and further, the lack of radiation exposure offers a unique advantage over nuclear medicine techniques, that is, the ability to image patients multiple times without limit. This may be especially useful for longitudinal studies, and in following the effects of pharmacologic interventions. Patients with neurologic disorders, such as those in this report, routinely undergo MR imaging for diagnostic purposes, so the addition of only a few minutes to the scanning procedure adds minimal additional inconvenience and cost.

These preliminary results are potentially promising but must be viewed with caution. The sample is small, and the method is in its infancy. Much more work on a larger series of healthy volunteers and patients with neurologic disorders is needed before the potential clinical use of this technique can be objectively evaluated. In particular, improvements in SNR and curve-fitting procedures will be essential, as will likely hardware modifications.

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